II. REMARKS/ARGUMENTS

A. Status of Claims/Specification

Claims 38 and 47-53 are currently pending. Claims 1-37 and 39-46 were previously cancelled. No amendments have been made herein.

B. Rejection under 35 U.S.C. 103 (a) over Baker et al., Swingle et al. and/or Rabasseda

In the Office Action, the Examiner rejected claims 38, 47-48 and 50-53 under 35 U.S.C 103 (a) over US 4,569,937 (hereinafter "Baker"), Swingle et al. Drugs Exptl. Clin, Res. Vol. X (8-9) (1984) (hereinafter "Swingle") and/or Rabasseda, Drugs of Today Vol. 32, No. 5 (1996) pages 365-384 (hereinafter "Rabasseda").

a. There is no motivation to substitute the ibuprofen in the synergistic combination of the Baker composition with another NSAID

Applicants respectfully submit that the combination of the Baker and Swingle and/or Rabasseda references fail to provide the motivation to one of ordinary skill in the art to substitute the ibuprofen in the Baker formulation with any other NSAID, let alone nimesulide, as discussed in the Swingle and Rabasseda references.

The Baker reference teaches a synergistic combination of narcotic analgesics and ibuprofen. It appears that the Examiner is overlooking the fact that the Baker reference utilizes ibuprofen because of its enhanced analgesic effect it has with oxycodone. There is nothing in the Swingle and Rabasseda references to suggest that nimesulide would have this effect also, therefore there is no motivation to substitute the ibuprofen in the Baker composition with nimesulide. Applicants respectfully point out that the purported invention of the Baker reference is directed to pharmaceutical compositions of narcotic analgesics and ibuprofen which "... exhibit unexpectedly enhanced analgesic activity ..." (See Abstract). The Baker reference is therefore limited to combinations wherein the NSAID is ibuprofen and does not teach or suggest

that the purported "unexpectedly enhanced analgesic activity" would occur with an NSAID which is different than ibuprofen.

Applicants further submit that, in view of the above, the Baker reference teaches away from substituting ibuprofen with another NSAID (e.g., nimesulide), because of the unexpected synergy that it purports for the combination of ibuprofen with a narcotic analgesic. Accordingly, due to this purported synergy, one skilled in the art would be discouraged to combine the Baker reference with the Swingle and/or Rabasseda references in order to select an NSAID different than ibuprofen (i.e., nimesulide) to combine with oxycodone. "A prior art reference may be considered to teach away when 'a person of ordinary skill, upon reading the reference would be discouraged from the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998). Therefore, Applicants submit that, as a whole, the Baker reference would steer one of ordinary skill in the art away from combining the Baker reference with the Swingle and Rabasseda references to select an NSAID different than ibuprofen (i.e., nimesulide) to combine with oxycodone, for the reasons argued above.

In addition, Applicants submit that modifying the formulation of the Baker reference in view of Swingle and Rabasseda references, as proposed by the Examiner, by substituting ibuprofen with nimesulide would result in a dosage form which is not directed to the principle of operation described in the Baker reference (i.e., the purported synergism of narcotic analgesics and ibuprofen). "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." See MPEP 8th edition, Revision 2, p.2100-132.

b. The reference to NSAIDs in the Background of the Invention in the Baker reference specifically refers to the limited compounds in the Sunshine reference which do not include nimesulide

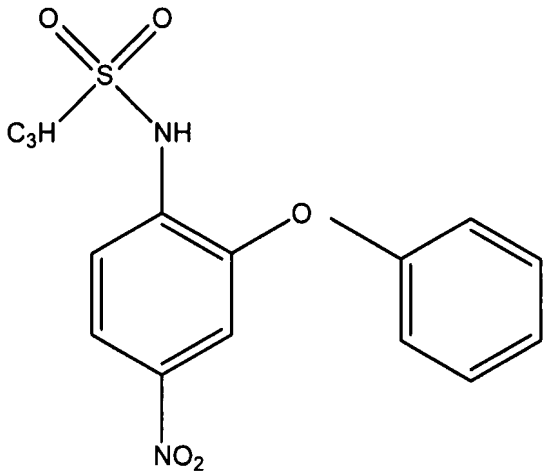
In the June 19, 2006 Final Office Action, the Examiner referenced column 1, lines 23-25 of Baker which recites "[t]his patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone". Based on this statement, the Examiner concluded that "Baker et al. teach the entire genus of NSAIDs plus narcotic analgesic as providing beneficial analgesia." However, Applicants respectfully point out that the phrase "this patent" in column 1, line 23 of the Baker reference actually refers to U.S. Patent No. 4,464,376 issued to A. Sunshine et al. (hereinafter "the Sunshine reference"). The two references to the term "NSAID" at column 1, lines 17-27, are the only recitations of the term "NSAID" in the entire patent, and they are with reference to the teachings of the Sunshine reference. Therefore, Applicants submit that the only NSAIDs taught by the Baker reference are those taught by the Sunshine reference, which is not inclusive of the "entire genus of NSAIDs" as alleged by the Examiner.

Applicants point to the Sunshine reference at column 14, lines 58-61, which recite "[t]he term 'selected NSAID' as used herein is intended to mean any non-narcotic analgesic/nonsteroidal anti-inflammatory compound **falling within one of the five structural categories indicated hereinabove.**" (Emphasis added).

These five categories are set forth at column 7, lines 42-50 of the Sunshine reference which states that:

> The non-narcotic analgesics/nonsteroidal anti-inflammatory drugs for use in the compositions and methods of the present invention can be selected from the following categories:
> (1) the propionic acid derivatives;
> (2) the acetic acid derivatives;
> (3) the fenamic acid derivatives;
> (4) the biphenylcarboxylic acid derivatives; and
> (5) the oxicams.

The chemical structures of the (5) categories are exemplified in columns 8-11. Applicants submit that the chemical structure of the presently claimed NSAID, *i.e.* nimesulide:



does not fall within any of the five structural categories indicated above. Therefore, even assuming arguendo that the Baker reference contemplates the use of other NSAIDs based on the reference to the Sunshine reference, Applicants submit that the "other" NSAIDs would be limited to the five structural categories listed in Sunshine and would not include nimesulide.

Further, Applicants respectfully submit that it is improper for the Examiner to rely solely on the Background of the Invention of the Baker reference and ignore the further teaching of this reference. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Accordingly, it is Applicants' position that when evaluated as a whole, the Baker reference teaches that ibuprofen provides a synergistic effect in combination with narcotic analgesics and therefore leads away from substituting the ibuprofen with nimesulide as suggested by the Examiner.

Therefore, it is Applicants position that the Baker reference as a whole does not teach or suggest the use of any NSAIDs other than ibuprofen, as the only mention of "NSAIDs" is in

the "Background of the Invention". However, even assuming arguendo that the Baker reference teaches other NSAIDs, Applicants submit that the "other" NSAIDs would not include nimesulide as discussed above with reference to the Sunshine reference.

c. The Swingle and Rabasseda references do not definitively conclude that nimesulide is equally efficacious with less side effects than ibuprofen

In the prosecution history of the present application, the Examiner concluded that "the Swingle et al. and/or Rabasseda reference teachings that Nimesulide is more efficacious and safer with less side effects (e.g. as compared to other non-selective COX-2 inhibitor NSAID's i.e. ibuprofen)." September 29, 2005 Office Action. In making this conclusion, Applicants respectfully submit that the Examiner is relying on only certain portions of the Swingle and Rabasseda references, which do not compare nimesulide to ibuprofen. Therefore, Applicants respectfully submit that the Examiner is not considering the prior art references as a whole and is mischaracterizing the conclusions of the studies performed in the Swingle and Rabasseda references.

For example, the Examiner mischaracterized the Swingle reference by stating that the reference teaches "that Nimesulide...is four time more potent than indomethacin in anti-inflammatory rodent assays as compared to other NSAID's (including ibuprofen)," and cited to the Abstract and Figures 2-11 of the Swingle reference. Id. Applicants respectfully point out that, as admitted by the Examiner, the Abstract of the Swingle reference only compares nimesulide to indomethacin, not ibuprofen. Further, there is no comparison of nimesulide to ibuprofen with respect to therapeutic activity in the Swingle reference. Therefore, Applicants respectfully submit that absent a comparison of therapeutic activity, one skilled in the art would not be motivated to substitute ibuprofen with nimesulide in the formulations of the Baker reference. Applicants especially submit that this is especially true when the ibuprofen provides a synergistic effect when combined with opioid analgesics as purported in the Baker reference.

Additionally, the Examiner mischaracterized the Rabasseda reference by stating that the references teaches "that Nimesulide is a sulfonamide NSAID that possesses potent anti-inflammatory, analgesic and antipyretic activates in a wide-range of animal experimental models and a potent and specific inhibitor of [COX-2] and as such has a much lower risk of gastroduodenal lesions in comparison with other NSAID's, including ibuprofen. E.g. see pages 365 and 374-377." September 29, 2005 Office Action. However, Applicants respectfully point out that page 364 of the Rabasseda reference does not mention ibuprofen, as improperly suggested by the Examiner, but rather only mentions the term "NSAIDs" in general. Moreover, ibuprofen is not included in the listing of "reference NSAIDs" on page 374[1] which were used in the comparative studies. Therefore, it is improper for the Examiner to assume that the comparative results discussed in the Rabasseda reference would be applied to ibuprofen.

When viewing the Swingle and Rabasseda references in their entireties, Applicants submit that that these references do not definitively conclude that nimesulide is equally efficacious and safer with less side effects than ibuprofen, as improperly construed by the Examiner. Therefore, Applicants submit that the references fail to provide the motivation to substitute nimesulide for the ibuprofen utilized in the Baker reference.

To further support the position that the cited references do not definitively conclude that nabumetone has less side effects than ibuprofen, the Examiner is directed to page 374 of the Rabassa reference which states that 6% of the reported adverse reactions were adverse reactions to the skin. However, it is reported in the Eversmeyer reference (Exhibit A) that rash was 0.9% of the reported adverse effects for ibuprofen. Therefore, even though it is purported in the Swingle reference that ibuprofen has an intermediate relative ulcerogenic activity as compared to low ulcerative activity for nimesulide (see Fig. 10 of Swingle), the Rabassa reference (in view of the Eversmeyer reference) appears to indicate that ibuprofen has a better adverse event profile for skin effects as compared to nimesulide. Therefore, due to the indication that either nimesulide or ibuprofen appear to be better tolerated by patients depending on the

[1] Reference NSAIDs include: piroxicam, ketoprofen, naproxen, etodolac, paracetamol, diclofenac, lysine salicylate, mefenamic acid and metamizole. See Rabasseda at page 373 and 374, Figure 6.

specific side effect, Applicants submit that these references do not definitively conclude that nimesulide is safer with less side effects than ibuprofen

d. The Examiner is relying on an improper "obvious to try" rationale

Applicants submit that the Examiner is applying an improper "obvious to try" rationale in suggesting the substitution of ibuprofen with nimesulide. "In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir.1988). Applicants submit that *In re O'Farrell* is analogous to the present situation, where one of ordinary skill in the art would have to try each of numerous possible NSAIDs in place of ibuprofen in order to arrive at the selection of nimesulide, as the Baker reference gives no direction as to what NSAIDs other than ibuprofen would be successful.

e. The Examiner is improperly picking and choosing ibuprofen and oxycodone from the prior art

Applicants submit that the Examiner is improperly picking and choosing the nimesulide of the Swingle and Rabasseda references and the oxycodone of the Baker reference to recreate the claims of the present application. One "...cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention." *SmithKline Diagnostics, Inc. v. Helena Laboratories Corporation*, 859 F.2d 878, 887 (Fed. Cir. 1988).

Based on Applicants review of the Baker reference, it appears that the inventors in the Baker reference rejected all NSAIDs in their invention *except* ibuprofen. The purported invention and teachings of the Baker reference are limited to the combination of a narcotic

analgesic and ibuprofen. For example, column 1, lines 6 - 9 of the Baker reference states as follows:

> *This invention relates to pharmaceutical compositions of narcotic analgesics and ibuprofen having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals.*
> (Emphasis Added)

Column 2, lines 11-15 of the Baker reference states as follows:

> *According to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof,...*
> (Emphasis Added)

The following additional passages from the Baker reference are also limited to a combination of narcotic analgesics and ibuprofen:

Column/Lines	**Text**
Title:	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Abstract:	ABSTRACT Pharmaceutical compositions of narcotic analgesics and ibuprofen . . .
Figure 1	ISOBOLOGRAM FOR THE INTERACTION OF ORAL OXYCODONE HCL AND IBUPROFEN . . .
Col. 1, line 1 & 2	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Col. 2, lines 20-24	. . . synergistically effective analgesic amounts of oxycodone, or a pharmaceutically suitable salt thereof, and ibuprofen, or a pharmaceutically suitable salt thereof . . .
Col. 2, line 34 & 35	. . . various dose ratios of oxycodone and ibuprofen.
Col. 2, lines 64 & 65	In a composition of the invention, oxycodone and ibuprofen are combined . . .
Col. 3, lines 23 & 24	. . . unexpectedly enhanced analgesic activity of combinations of oxycodone and ibuprofen . . .

Column/Lines	Text
Col. 3, lines 53-56	. . . the active ingredient is administered at a daily dosage of from about 0.05 to 7.50 milligrams per kilogram (mg/kg) of body weight of oxycodone and from about 10 to 120 mg/kg of ibuprofen.
Col. 4, lines 24-29	Example 1 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 4, lines 36-42	Example 2 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 300.0
Col. 4, lines 48-55	Example 3 Oxycodone/Ibuprofen Tablets Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 4, lines 60-66	Example 4 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 5, lines 8-14	Example 5 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 300.00
Col. 5, lines 20-26	Example 6 Oxycodone/Ibuprofen Capsules Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 5, lines 33-39	Example 7 Oxycodone/Ibuprofen Tablets Oxymorphone HCl 5.0 Ibuprofen 60.0
Col. 5, lines 45-51	Example 8 Oxymorphone/Ibuprofen Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 5, lines 58-63	Example 9 Oxymorphone/Ibuprofen Oxymorphone HCl 2.5 Ibuprofen 300.0

Column/Lines	Text
Col. 6, lines 1-7	Example 10 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 60.0
Col. 6, lines 13-19	Example 11 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 6, lines 25-31	Example 12 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 38-43	Example 13 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 6, lines 49-55	Example 14 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 6, lines 61-66	Example 15 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 9-14	Example 16 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 7, lines 21-27	Example 17 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 7, lines 33-39	Example 18 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 46-51	Example 19 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 60.0

Column/Lines	Text
Col. 7, lines 57-63	Example 20 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 300.0
Col. 8, lines 1-7	Example 21 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 13-19	Example 22 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 8, lines 26-31	Example 23 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 300.0
Col. 8, lines 37-43	Example 24 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 56-58	All mice are dosed sequentially by the oral route with suspensions of ibuprofen and/or oxycodone hydrochloride solutions.
Col. 8, line 62	A stock suspension of ibuprofen is . . .
Col. 9, lines 22-24	Mice, intubated with various doses of oxycodone hydrochloride, ibuprofen, combined doses of oxycodone hydrochloride and ibuprofen . . .
Col. 9, lines 45-47	In order to study the interaction between oxycodone and ibuprofen, 5 precise dosage ratios of oxycodone hydrochloride and ibuprofen are selected.
Col. 10, lines 25 & 26	The synergistic interaction of oxycodone hydrochloride and ibuprofen . . .
Col. 10, lines 29-31	. . . the analgesic effect of oxycodone along is presented in the ordinate, and that of ibuprofen alone is on the abscissa.
Col. 10, lines 32-34	. . . exact fixed dosage ratios based on weight of oxycodone HCl:ibuprofen in the ranges of 1:1.25 to 1:31.1.
Col. 10, lines 35 & 36	. . . representing oxycodone and ibuprofen alone . . .
Col. 10, lines 36-38	. . . representing the compositions of oxycodone and ibuprofen at the fixed dosage ratios.
Col. 11, lines 31-33	. . . straight line additivity hypothesis for oxycodone HCl and ibuprofen . . .
Col. 12, lines 52-54	. . . analgesic synergism is established for all combinations of oxycodone and ibuprofen.

Column/Lines	Text
Col. 12, lines 55 & 56	By substitution of the expected analgesic activity of oxycodone alone and ibuprofen alone . . .
Col. 12, lines 62 & 63	. . . it is predicted that oxycodone and ibuprofen would demonstrate analgesic potentiation . . .
Table 1	TABLE 1 ORAL OXYCODONE HCl/IBUPROFEN COMBINATIONS Oxycodone Ibuprofen Oxycodone Ibuprofen
Col. 13, lines 49-55	1. A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:6 to about 1:400.

As evidenced above, ibuprofen is the only NSAID mentioned throughout the entire reference, and it is the only NSAID exemplified in the Baker formulations.

f. The Examiner is improperly relying on In re Kerkhoven

The Examiner also stated that "[a]s set forth in *In re Kerkhoven*, it is *prima facie* obvious to combine two (or more) compositions, each of which is taught by the prior art, in order to form a third composition to be used for the very same purpose (i.e. pain management of analgesia)." (Emphasis Added)(Citations omitted).

The fact that the Swingle and Rabasseda references discuss the benefits of nimesulide over other NSAIDs does not provide the requisite motivation to substitute the ibuprofen of the Baker reference, when the Baker reference visibly contemplates only ibuprofen. Further, even when read in the most favorable light to use NSAIDs other than ibuprofen, a position which the Applicants do not support, the suggestion of other NSAIDs must be interpreted in view of the teachings of the Sunshine reference, which exclude the use of nimesulide.

Therefore, Applicants respectfully submit that the Examiner's statements indicate that *In re Kerkhoven* is not being properly applied in rejecting the present claims. As stated by the Examiner, the holding of *In re Kerkhoven* is with respect to combining references. However, the

Examiner's rejection, is based on modifying the Baker analgesic composition. Applicants respectfully submit that a combination of the Baker analgesic composition with nimesulide would result in a formulation including a combination of nimesulide and ibuprofen and an opioid analgesic, and therefore would not result in the presently claimed invention.

C. Rejection under 35 U.S.C. 103 (a) over Baker et al., Swingle et al. and/or Rabasseda in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)

In the Office Action, the Examiner further rejected claim 49 under U.S.C. 103 (a) over Baker et al., Swingle et al. and/or Rabasseda in view of US 5,472,712 (Oshlack et al.) and US 6,294,195 (Oshlack et al.)

Applicants respectfully submit that, for the reasons discussed above, the Baker reference, the Swingle reference and the Rabasseda reference fail to teach or suggest the presently claimed method of effectively treating pain by administering a combination of two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) nimesulide and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof.

Applicants further submit that the Oshlack references also fail to teach or suggest the presently claimed method of effectively treating pain by administering a combination of analgesic compounds consisting essentially of (i) nimesulide and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof.

Accordingly, as the Oshlack references fail to cure the deficiencies of the Baker, Swingle and Rabasseda references, Applicants respectfully request that the rejections over the Baker, Swingle and Rabasseda references in view of either Oshlack references be removed.

IV. CONCLUSION

In view of the foregoing, it is believed that the application is now in condition for allowance, and applicants respectfully request such action.

The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Applicants note that a Notice of Appeal was filed and received by the Patent Office on January 27, 2007. Therefore, a response is due July 27, 2007 with a four-month extension of time. Accordingly, this response is being filed on July 27, 2007 concurrently with a Request for Continued Examination, a Petition for a four-month extension of time and associated fees.

Respectfully submitted,
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